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Female sex reduces the risk of hospital-associated acute kidney injury: a meta-analysis

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Abstract

Background: Female sex has been included as a risk factor in models developed to predict the development of AKI. In addition, the commentary to the Kidney Disease Improving Global Outcomes Clinical Practice Guideline for AKI concludes that female sex is a risk factor for hospital-acquired AKI. In contrast, a protective effect of female sex has been demonstrated in animal models of ischemic AKI.

Methods: To further explore this issue, we performed a meta-analysis of AKI studies published between January, 1978 and April, 2018 and identified 83 studies reporting sex-stratified data on the incidence of hospital-associated AKI among nearly 240,000,000 patients.

Results: Twenty-eight studies (6,758,124 patients) utilized multivariate analysis to assess risk factors for hospital-associated AKI and provided sex-stratified ORs. Meta-analysis of this cohort showed that the risk of developing hospital-associated AKI was significantly greater in men than in women (OR 1.23 (1.11,1.36). Since AKI is not a single disease but instead represents a heterogeneous group of disorders characterized by an acute reduction in renal function, we performed subgroup meta-analyses. The association of male sex with AKI was strongest among studies of patients who underwent non-cardiac surgery. Male sex was also associated with AKI in studies which included unselected hospitalized patients and in studies of critically ill patients who received care in an intensive care unit. In contrast, cardiac surgery-associated AKI and radiocontrast-induced AKI showed no sexual dimorphism.

Conclusions: Our meta-analysis contradicts the established belief that female sex confers a greater risk of AKI and instead suggests a protective role.

Keywords: Acute kidney injury, Gender, Meta-analysis, Systematic review, Acute renal failure

Background

Sexual dimorphism is a well-established feature of chronic progressive kidney disease [1]. Although less well recognized, sexual dimorphism has also been established in the development of ischemic acute kidney injury (AKI) [2]. Animal models have consistently demonstrated that female sex is protective in the development of AKI after ischemia-reperfusion injury [2–14]. Despite these experimental observations, it has been suggested that the direction of sexual dimorphism is reversed in humans with AKI. Female sex has been included as a risk factor in models developed to predict the risk of AKI associated with cardiac surgery, aminoglycoside nephrotoxicity, rhabdomyolysis and radio-contrast administration [15–18]}. The commentary to the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury (arguably the most authoritative commentary in the field) states that female sex is among the "shared susceptibility factors" that confer a higher risk of AKI [19]. This conclusion is based on observations that female sex is associated with a higher risk for AKI after cardiac surgery and after the administration of radio-contrast or aminoglycosides. On this basis, the commentary concludes that, "contrary to most chronic kidney disease disorders, it is the female gender that carries a higher risk for AKI." This conclusion, however, is qualified by the observation that

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males predominate in reports of AKI complicating infections with HIV, malaria, leptospirosis and other community-acquired forms of AKI.

We have previously challenged the generally held consensus that female sex is an independent risk factor for cardiac surgery-associated AKI and for aminoglycoside nephrotoxicity [18, 20]. In the present study, we sought to explore the relationship between sex and hospital-associated AKI (HAAKI) in greater detail by performing a systematic review and meta-analysis of studies published between January, 1978 and April, 2018 which report the sex-stratified incidence of HAAKI.

Methods

Search strategy and selection criteria

We conducted a systematic review and meta-analysis of the English literature to evaluate the reported incidence of acute kidney injury in hospitalized women versus hospitalized men. Our analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocol [21].

We searched PubMed for English-language articles published between January 1, 1978 and April 1, 2018. The following medical subject heading terms were used: male, female, sex, gender, acute kidney injury, and acute renal failure. EMBASE was also queried with the terms sex difference, acute kidney injury and acute renal failure. Titles and abstracts of articles found in the database search were reviewed to identify eligible studies. Full text versions of selected studies were analyzed in detail. We also examined the bibliographies of recovered articles for additional resources. Any case control or cohort study of 10,000 or more hospitalized patients in which the sex-stratified incidence of AKI was reported was eligible for inclusion (Fig. 1). To determine study quality, the studies were assessed using the Newcastle Ottawa Score for cohort and case control studies [22].

Definition of AKI

Hospital-associated AKI was defined as AKI that developed in hospitalized patients. This definition included patients who developed AKI within the first 48 h of admission to the hospital (community-acquired AKI) and patients who developed AKI later during their hospital course (hospital-acquired). We accepted studies that defined AKI by investigator-created, creatinine-based criteria, Acute Kidney Injury Network (AKIN) criteria, Kidney Disease: Improving Global Outcomes (KDIGO) criteria, Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease (RIFLE) criteria, or by the requirement for renal replacement therapy (AKI-D) [19, 23, 24].

Data extraction

All studies were examined for duplication of data. Attention was given to the reporting clinical centers, years covered, and overlap with larger regional or national databases. In the case of overlap, a weighting factor was assigned to the smaller study that was inversely proportional to the degree of overlap. If the weighted number of patients fell below 10,000, the study was excluded. We also excluded studies with less than 25 AKI events among either of the sexes.

We separated the selected studies in to 2 groups. The first group included studies in which the investigators utilized multivariate analysis and reported adjusted odds ratios. The second group included studies in which unadjusted data was reported.

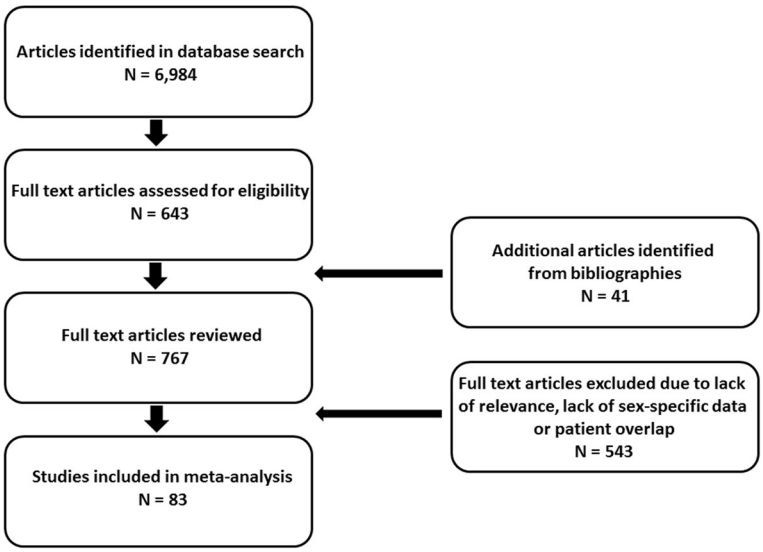

Fig. 1 Flow diagram describing the identification of studies included in the meta-analysis

We analyzed separately studies restricted to patients who underwent radio-contrast procedures (percutaneous coronary interventions or computerized axial tomography) but which failed to specify whether the procedure was performed in an ambulatory care setting or was associated with an in-patient hospital stay. In this regard, most computerized axial tomography procedures are performed in an out-patient rather than in an in-patient setting and percutaneous coronary interventions have moved from an exclusively in-patient procedure to a predominantly ambulatory procedure over the last decade (0% ambulatory in 2009 to 77% ambulatory in 2015) [25].

Statistical analysis

Data were analyzed using a random effects model with RevMan Version 5.3, The Cochrane Collaboration 2014. Meta-regression analysis and sub-group meta-analysis were performed with OpenMetaAnalyst 2016 [26].

Results

Adjusted analyses

Twenty-eight studies (6,758,124 patients; 2,313,202 women and 4,444,922 men) utilized multivariate analysis to assess risk factors for hospital-associated AKI and provided sex-stratified ORs (Fig. 2) [27–53]. Eight studies included only hospitalized patients who underwent cardiac surgery, 10 studies included only hospitalized patients who underwent predominantly non-cardiac surgery, 3 studies included only critically ill patients who received care in an intensive care unit, 6 studies included unselected hospitalized patients, whereas the remaining study included only hospitalized patients with a diagnosis of acute decompensated heart failure. AKI was defined by KDIGO criteria in 10 studies, by RIFLE criteria in 1 study, by AKIN criteria in 2 studies, by the need for renal replacement therapy in 7 studies, and by investigator-created, creatinine-based criteria in the remaining 8 studies. Nearly all studies that utilized RIFLE, AKIN or KDIGO criteria to define AKI relied solely on serum creatinine criteria rather than urine output criteria.

Meta-analysis of this cohort showed that men were significantly more likely to develop HAAKI than women (OR 1.23 (1.11,1.36), $n = 28$ studies, 6,758,124 patients).

We observed a high degree of statistical heterogeneity in the meta-analysis ($I^2 = 98.0\%$, $p < 0.001$). This is not surprising since AKI is not a single disease but instead represents a heterogeneous group of disorders characterized by an acute reduction in renal function. To evaluate the source of statistical heterogeneity, we performed a regression meta-analysis and subgroup analyses.

We found that statistical heterogeneity was related to the criteria used to select the study cohort and to the

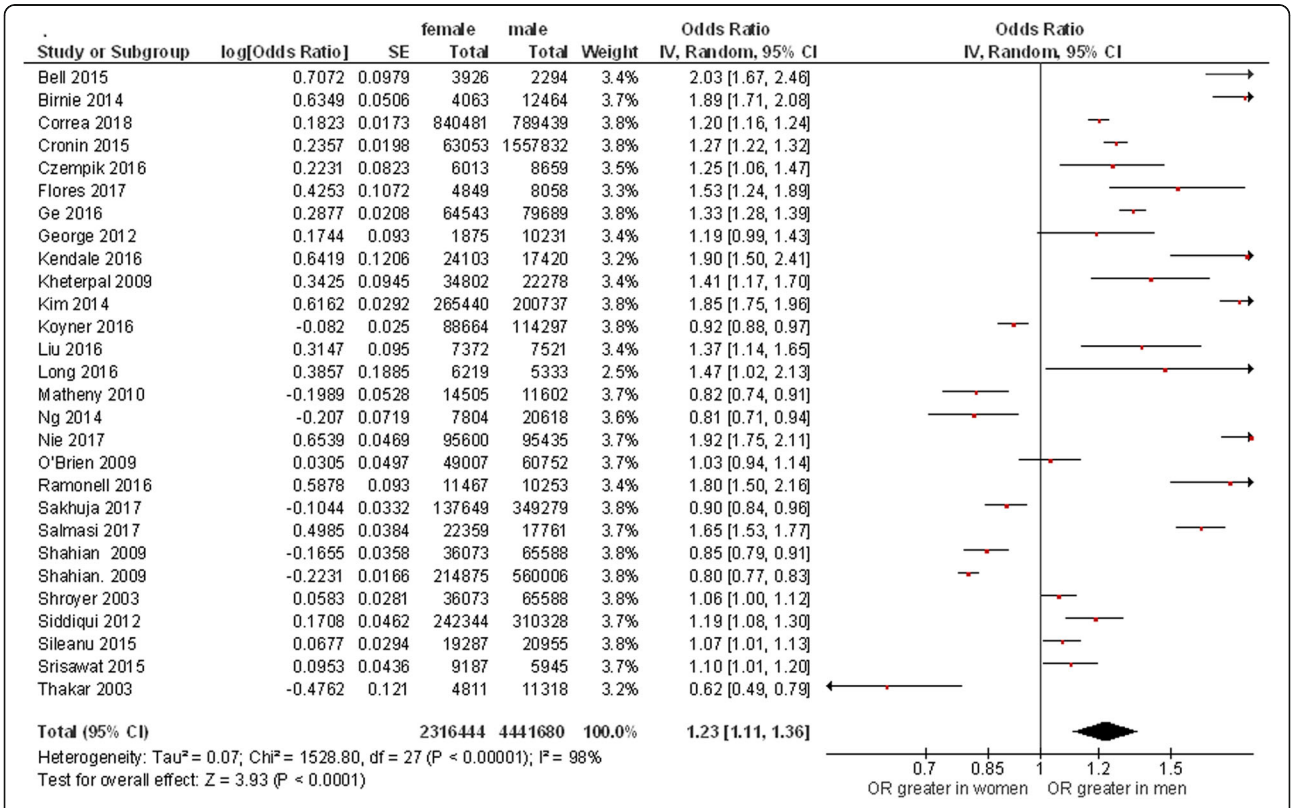

Fig. 2 Meta-analysis of 28 studies that provided adjusted sex-stratified data regarding the incidence of hospital-associated AKI

criteria used to define AKI, but was not related to year of publication, number of AKI events or total number of patients studied. The association of male sex with the development of AKI was strongest among studies restricted to patients who underwent predominantly non-cardiac surgery (OR 1.56 (1.37,1.77), $n = 10$ studies, 1,225418 patients, 606,881 women and 618,537 men). Male sex was also associated with AKI in studies of unselected hospitalized patients (OR 1.22 (1.01,1.49), $n = 6$ studies, 2,196,772 patients, 332,584 women and 2,196,772 men), and in studies of critically ill patients who received care in an intensive care unit (OR 1.10 (1.03,1.18), $n = 3$ studies, 70,046 patients, 34,487 women and 35,559 men). In contrast, cardiac surgery-associated AKI showed no sexual dimorphism (OR 0.95 (0.80,1.13), $n = 8$ studies, 1,635,968 patients, 490,355 women and 1,145,613 men).

The sex-stratified incidence of HAAKI also varied according to the criteria used to define AKI. Men were more likely to develop HAAKI than were women when AKI was identified by KDIGO criteria (OR 1.38 (1.19,1.59), $n = 10$ studies, 2,263,679 patients, 361,914 women and 1,901,765 men), and by AKIN criteria (OR 1.69 (1.52,1.88), $n = 2$ studies, 81,643 patients, 46,462 women and 35,181 men). There was no difference in the incidence of HAAKI between the sexes when AKI was identified by the need for renal replacement therapy (OR 1.05 (0.92, 1.10), $n = 7$ studies, 2,822,186 patients, 1,282,180 females and 1,540,006 men) or by investigator-created, creatinine-based criteria (1.19 (0.91, 1.55), $n = 8$ studies, 1,564,509 patients, 611,383 women and 953,126 men).

In a separate analysis, the incidence of AKI among adjusted studies of patients who underwent percutaneous coronary interventions or computerized axial tomography was equivalent in men and women (OR 1.05 (0.79,1.40), $n = 3$ studies, 1,087,879 patients, 347,811 women and 740,068 men) [54–56].

Unadjusted analyses

The unadjusted cohort consisted of 68 studies which included 232,586,252 patients (130,605,382 women and 101,970,870 men (Figs. 3 and 4) [29, 31–34, 36, 38, 42, 43, 45, 47, 57–112]. Studies could be divided into 7 distinct categories. Twenty-four studies included unselected hospitalized patients, 11 studies included only hospitalized patients who underwent cardiac surgery, 13 studies included only hospitalized patients who underwent predominantly non-cardiac surgery, 11 studies included only critically ill patients who received care in an intensive care unit, whereas the remaining 9 studies included hospitalized patients selected based on their underlying disease (liver disease, cerebrovascular disease, human immunodeficiency virus infection, congestive heart failure, or atrial fibrillation). AKI was defined by RIFLE criteria in 5 studies, by AKIN criteria in 11 studies, by KDIGO criteria in 17 studies, by the need for renal replacement therapy in 20 studies, and by investigator-created, creatinine-based criteria in the remaining 15 studies. Nearly all studies that utilized RIFLE, AKIN or KDIGO criteria to define AKI relied solely on serum creatinine criteria rather than urine output criteria.

Meta-analysis of the entire cohort of unadjusted studies showed that men were significantly more likely to develop HAAKI than women (OR 1.29 (1.18,1.42), $n = 68$ studies, 232,586,252 patients). We observed a high degree of statistical heterogeneity in this analysis ($I^2 = 99.6\%$, $p < 0.001$). This is not surprising since AKI is not a single disease but instead represents a heterogeneous group of disorders characterized by an acute reduction in renal function. To evaluate the source of statistical heterogeneity, we performed a regression meta-analysis and subgroup analyses. We found that statistical heterogeneity was related to the criteria used to select the study cohort and to the criteria used to define AKI, but was not related to year of publication, number of AKI events or total number of patients.

The association of male sex with the development of AKI was strongest among studies reporting unadjusted data from patients undergoing predominantly non-cardiac surgery (OR 1.63 (1.34,1.97), $n = 13$ studies, 556,647 patients, 246,136 women and 310,511 men) and among studies of unselected hospitalized patients (OR 1.52 (1.34,1.70), $n = 24$ studies, 224,740,578 patients, 127,168,880 women and 97,571,698 men). Male sex was also associated with AKI among studies in which patients were selected based on a disease-specific diagnosis (1.31 (1.04,1.65), $n = 9$ studies, 4,055,606 patients, 1,919,721 women and 2,135,885 men). In contrast, among unadjusted studies of cardiac surgery-associated AKI, AKI was less frequent in men than in women (OR 0.82 (0.74, 0.91), $n = 11$ studies, 1,413,349 patients, 398,205 women and 1,015,144 men). The incidence of AKI among critically ill patients who received care in an intensive care unit was similar in men and women (OR 1.05 (0.89,1.25), $n = 11$ studies, 1,774,707 patients, 846,347 women and 928,460 men).

The unadjusted sex-stratified incidence of HAAKI also varied according to the criteria used to define AKI. Men were more likely to develop HAAKI than were women when AKI was identified by KDIGO criteria (OR 1.34 (1.20,1.51), $n = 17$ studies, 1,804,815 patients, 868,140 women and 936,675 men), or by the need for renal replacement therapy (OR 1.33 (1.17,1.50), $n = 20$ studies, 217,375,505 patients, 128,841,628 women and 98,533,877 men). In contrast, men were less likely to develop HAAKI than were women when AKI was identified by RIFLE criteria (OR 0.89 (0.82,0.96), $n = 5$ studies, 260,132 patients, 112,564 women and 157,568 men). There was no significant difference in the incidence of HAAKI between the sexes when AKI was identified by AKIN criteria (OR 1.23 (0.98,1.54), n = 11 studies, 1,783,778 patients, 286,062

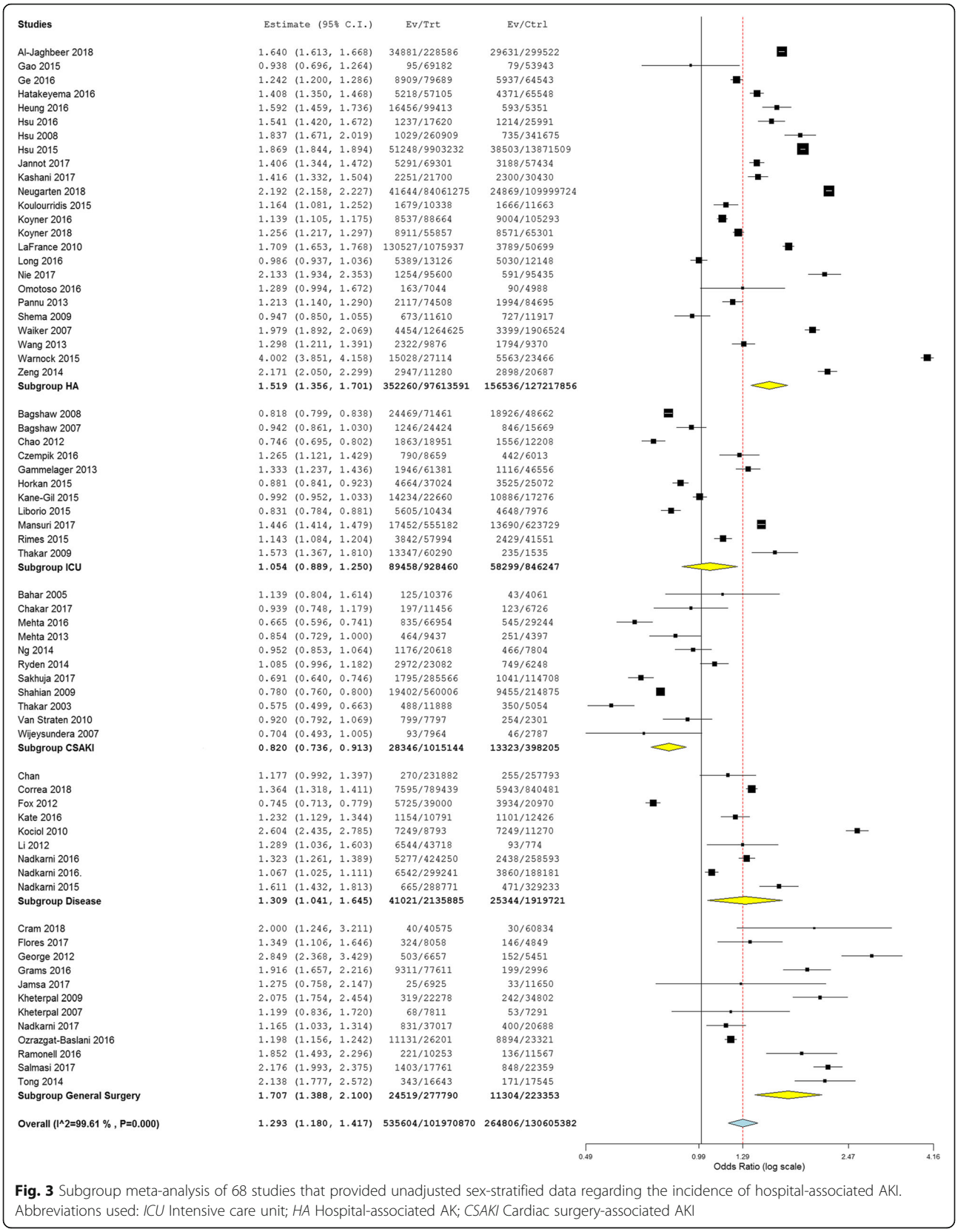

Fig. 3 Subgroup meta-analysis of 68 studies that provided unadjusted sex-stratified data regarding the incidence of hospital-associated AKI. Abbreviations used: *ICU* Intensive care unit; *HA* Hospital-associated AK; *CSAKI* Cardiac surgery-associated AKI

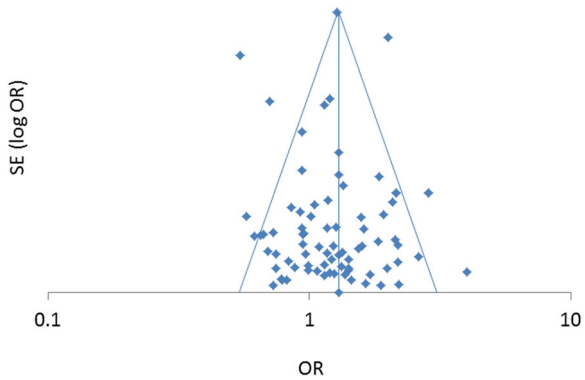

Fig. 4 Funnel plot of studies that analyzed risk factors for hospital-associated AKI and provided sex-stratified odds ratios

women and 1,497,716 men) or by investigator-created, creatinine-based criteria (OR 1.37 (0.92, 2.03), $n = 15$ studies, 1,306,657 patients, 470,795 women and 835,862 men).

In a separate analysis of unadjusted studies, radiocontrast-induced AKI in patients undergoing computerized axial tomography or percutaneous coronary interventions was less frequent in men than in women (OR 0.79 (0.69,0.90), $n = 9$ studies, 1,516,807 patients, 478,719 women and 1,038,088 men).

Discussion

Sexual dimorphism is a well-recognized feature of chronic progressive kidney disease [1]. Although less well recognized, sexual dimorphism has also been clearly established in AKI [2]. In contrast to CKD, where female sex is reno-protective, the direction of sexual dimorphism has been reported to be reversed in hospital-acquired AKI with female sex being associated with the development of AKI [19]. Moreover, female sex has been included as a risk factor in models developed to predict the risk of AKI associated with cardiac surgery, aminoglycoside nephrotoxicity, rhabdomyolysis and radio-contrast administration [15–18]. On the basis of these observations, the commentary to the KDIGO Clinical Practice Guideline for Acute Kidney Injury concludes that female sex is a risk factor for hospital-acquired AKI, while recognizing that male sex predominates in certain forms of community-acquired AKI. In the present study, we clearly show that it is male sex, not female sex, that is a risk factor for HAAKI, although we cannot determine whether this sexual dimorphism is driven by community-acquired or hospital-acquired AKI or both.

There is strong experimental basis to support our hypothesis that female sex is reno-protective in AKI [2–14, 20, 113]. Sexual dimorphism in AKI may be mediated by effects of sex hormones on cellular processes instrumental in the pathogenesis of AKI, analogous to our suggestion that sex hormones mediate sexual dimorphism in chronic kidney disease [1]. In experimental models of ischemic AKI, females show less severe renal functional impairment and less histologic damage after ischemia-reperfusion injury [2–14]. Numerous hypotheses have been proposed to explain these observations [2, 8, 113]. Sex-related differences in the generation of nitric oxide, in the synthesis and vascular response to endothelin-1, and in the renal hemodynamic response to angiotensin II have been demonstrated in experimental models and in human patients [2, 8]. Cellular responses to ischemia-reperfusion injury have also been shown to differ between the sexes. In response to ischemia-reperfusion, Na + -K+ ATPase enzyme activity is greater in females than in males and transcellular translocation of Na + -K+ ATPase is reduced [4]. Females subjected to ischemia-reperfusion injury maintain a reno-protective profile compared to their male counterparts with respect to heat shock protein HSP72, anti-oxidants such as superoxide dismutase, caspases and proteases involved in apoptosis, metalloproteinases such as meprin, inflammatory cytokines and members of signaling pathways that mediate pro-inflammatory responses [2–14, 113].

While our meta-analysis of adjusted studies demonstrated that, overall, female sex was associated with protection from HAAKI, our subgroup analysis revealed a relationship between the etiology of HAAKI and the presence or absence of sexual dimorphism. This is not surprising insofar as AKI is not a single disease but instead represents a heterogeneous group of disorders characterized by an acute reduction in renal function.

The association between female sex and protection from HAAKI was stronger among studies of hospitalized patients who underwent non-cardiac surgery than in the entire cohort of adjusted studies. Studies of critically ill patients receiving care in an intensive care unit and studies of unselected hospitalized patients also showed a higher incidence of AKI in men than in women. In this regard, unselected hospitalized patients better reflect the true relationship between sex and HAAKI as compared to studies in which patients were selected based on the etiology of AKI. In contrast, among studies of cardiac surgery-associated AKI, our meta-analysis demonstrated no difference between the sexes.

We have previously suggested that the association between female sex and cardiac surgery-associated AKI in unadjusted analyses reflects the greater burden of preexisting comorbidities among women undergoing cardiac surgery and does not indicate a greater intrinsic susceptibility of women to develop AKI under these circumstances [18]. This conclusion is reinforced by our demonstration in the present study that the sexual dimorphism associated with cardiac surgery-associated AKI in unadjusted analyses disappeared after adjustment for confounding factors.

It has been repeatedly demonstrated in unadjusted analyses and accepted by most authorities, including the commentary to the KDIGO Clinical Practice Guideline for AKI, that the incidence of contrast-induced nephropathy is greater in women than in men. However, some investigators have suggested that the association of contrast-induced nephropathy with female sex may merely reflects a higher dose of contrast administered to women compared to men [18]. Women generally have a lower body surface area than men, and accordingly the volume of administered contrast, when expressed as the volume of contrast administered per body surface area, has frequently been reported to be greater in women than in men. This hypothesis is consistent with our data which show that female sex was associated with contrast-induced nephropathy in unadjusted analyses, but that this association did not survive multivariate analysis.

We were surprised to find that only a modest, albeit significant, association of male sex with HAAKI in adjusted analyses of critically ill patients requiring care in an intensive care unit. Ischemic acute tubular necrosis is frequently the etiology of AKI in this setting and it is this form of renal injury that is most analogous to experimental ischemia-reperfusion injury, a model in which the reno-protection afforded by female sex is most robust [2–14].

A major limitation of our analysis relates to the inherent difficulty in defining AKI in men relative to women in light of sex-related differences in creatinine kinetics and the relationship of these differences to established criteria that define AKI. Waiker and Bonventre [114] assessed creatinine kinetics in patients with underlying chronic kidney disease and superimposed AKI. They identified differences in the sensitivity of absolute increases in serum creatinine levels versus relative increases in serum creatinine levels in identifying AKI in this population. They also emphasized the importance of the observation time in detecting threshold changes in serum creatinine levels. These observations are also relevant to comparisons of AKI incidence in men versus women. Since differences in the rate of generation and elimination of creatinine and in its volume of distribution exist between men and women with AKI, different criteria to define AKI might result in different sex-stratified incidence rates. Where AKI is defined by a percent change in the level of serum creatinine, the absolute change in creatinine needed to qualify as an AKI event is lower in women than in men since women generally have lower baseline serum creatinine levels. In contrast, where AKI is defined by an absolute increase in serum creatinine level, the percent change is serum creatinine required to qualify as an AKI event is greater in women than in men.

Also relevant to this issue are data reported by Srisawat et al. [52], which showed that the incidence of AKI was greater in men than in women when KDIGO criteria were used to define AKI, but that sex-related differences in the incidence of AKI disappeared when RIFLE criteria were used. These findings suggest that KDIGO criteria identify relatively more men than women with AKI compared to RIFLE criteria. Thus, it is possible that use of RIFLE criteria to define AKI, relative to KDIGO criteria, may mask the effect on female sex on the incidence of AKI, or conversely, that use of KDIGO criteria may magnify the effect. Consistent with this suggestion, our subgroup analysis shows that female sex was more likely to be associated with protection from AKI in those studies which utilized KDIGO criteria than in those that utilized RIFLE criteria. However, this conclusion is limited by the fact that our analysis, unlike the Srisawat data [52], compares outcomes based on differing definitions of AKI among different studies but not within an individual study.

We did not include in our meta-analysis 24 studies which utilized diagnosis codes to identify patients with non-dialysis-requiring AKI in the absence of corroborating biochemical data. Although Grams et al. [115] found a similar sensitivity and specificity for diagnosis codes in identifying AKI in men versus women, Waikar et al. [116] reported that the sensitivity was greater in men than in women. Were Waikar's data to apply, any conclusions about the relationship between sex and AKI identified by diagnosis codes would be placed in serious jeopardy. Incidentally, the incidence of AKI was greater in men than in women in nearly all of these studies.

In contrast, we included studies that relied on AKI-D data identified by diagnosis and procedure codes. Numerous studies have established the high sensitivity, specificity, positive predictive value and negative predictive value of diagnostic codes to identify AKI-D in a variety of administrative databases [115–119]. These indices generally exceeded 90% in all studies except that reported by Grams et al. [115]. Not only do diagnostic codes to identify AKI-D have a greater accuracy than those to identify AKI, they are also unlikely to be subject to miscoding based on the sex of the patient. Yet the fact remains that, despite the objective basis for dialysis coding, the actual decision to initiate dialysis by the clinician is a subjective one.

We recently performed a systematic review of dialysis practices in AKI and found no evidence that dialysis is initiated more often or earlier in men than in women with AKI of identical severity [120]. In fact, data exist to indicate the opposite, i.e. that dialysis is more aggressively pursued in women than in men despite identical severity of AKI. After propensity score matching of patients with AKI, Wilson et al. [121] reported that dialysis was more likely to be initiated in women than in men. Similarly, Chou et al. [122] utilized propensity matching of patients with sepsis and AKI treated in

surgical intensive care units and found that female sex was associated with earlier initiation of dialysis. Moreover, data from the North American Consortium for the Study of End-Stage Liver Disease indicates that hospitalized cirrhotic women are nearly twice as likely as men to receive renal replacement therapy despite similar median delta creatinine levels [123]. Thus, these studies suggest that the subjectivity inherent in the decision to initiate dialysis creates a bias that operates counter to our hypothesis, thereby strengthening our conclusion that the incidence of severe AKI requiring RRT is more common in men than in women.

Conclusions

A meta-analysis of studies providing sex-stratified incidence of HAAKI demonstrates that female sex is associated with protection from AKI. This finding undermines the established belief that female sex is a significant risk factor for AKI. On the contrary, and consistent with observations in animal models, it is male sex that is associated with HAAKI.

Abbreviations

AKI: Acute kidney injury; AKI-D: Acute kidney injury requiring dialysis; AKIN: Acute Kidney Injury Network; HAAKI: Hospital-associated acute kidney injury; KDIGO: Kidney Disease: Improving Global Outcomes; RIFLE: Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease (RIFLE); RRT: Renal replacement therapy

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Availability of data and materials

Available from the corresponding author on reasonable request.

Authors' contribution

All authors participated in the design and execution of the study and in drafting the manuscript. Both authors read and approved the final version.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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